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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,676	YANNI ET AL.	
	Examiner	Art Unit	
	Anoop K. Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 02/17/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-22 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating dry eye condition in a non human mammal, said method comprising administering to an eye of a non-human mammal a nucleic acid composition comprising a eukaryotic promoter operably linked to the nucleotide sequence disclosed in Seq ID No. 1 or 3 in an ocular drop, wherein the expression of said transgene resulting in treatment of dry eye condition, however it does not reasonably provide enablement for treating any patient, by any route of administration of any composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 encompasses a method for increasing the level of any therapeutic gene product in the condition of dry eye of any "patient", administered, via any route. The dependent claims 2-4 limit the composition to a vector comprising a nucleic acid

encoding the gene product or that the administration is topical using ocular drops or an ointment.

Claims 5-8, 14-17 include a method for increasing the level of a therapeutic gene product in of postmenopausal patient by incorporating nucleic acid expression in ocular cell that further limits to conjunctiva or corneal epithelial cells that is debrided under conditions permissive for the uptake of nucleic acid such that nucleic acid is expressed and patient is treated.

Claims 9-13 and 18-22 encompass viral vector and plasmid for delivering the gene to be expressed in ocular cell as claimed. The subsequent claims limit transgene in either retrovirus or adeno or adeno-associated virus.

The application as filed is not enabling for the invention commensurate with the full scope of the claims because art of targeting gene therapy in eye using any vector is unpredictable in human as has been recognized by the art of skill and therefore require undue experimentation. As will be shown below, these broad aspects as well as limitations were not enabled for the claimed invention commensurate with the full scope of the claims at the time of filling of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention commensurate with the scope of the claim.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by

weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

The aspects considered broad are: the breadth of any subject population subsequently limiting to postmenopausal patient, the breadth of any vector that could be used for treating dry eye condition subsequently limiting to few, any method of administration to affect eye subsequently limiting to drops or ointment, the increase of expression of transgene in many ocular cells then limiting to conjunctival or corneal epithelial cell and transgene not operably linked to expression control elements a critical limitation not described in claims.

The invention (claims 1-8, 15-17) encompassed increasing the levels transgene expression in eye of any subject subsequently limiting to postmenopausal patient via any route of administration subsequently limiting to topical application such that dry eye condition is treated. Additionally, the invention encompasses treating dry eye condition of postmenopausal patient, is interpreted to have use in the art for treating humans: e.g., in clinical trials or treatment.

The Nature of such Invention is within the broad genera of gene therapy, and gene therapy is not generally enabling of Applicant's invention due to problems with, *inter alia*, targeting and expression of transgenes at therapeutically effective level by any route in any specific tissue. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification broadly discloses the need for composition and treatment for dry eye condition particularly in postmenopausal women (pp. 2). The invention is based in part on the discovery that mucin reside in the apical and sub apical corneal epithelium which is secreted via cornea apical, sub apical cells and conjunctival epithelium of human eye (pp 4-5). Page-5 describes different part of the body that produces and secretes mucin and it briefly lists agents that increase mucin and/or tear production. Page-7 broadly tracks claim language. The present inventor discloses that ocular surface epithelium of postmenopausal women lack 15-lipoxygenase. This is required for the synthesis of 15(s)-HETE, which in turn stimulates the production of MUC-1 mucin (pp 8). Pages 9-13 broadly discuss role of lipoxygenase, *in situ* ocular cells, method and

type of vector and its use, target ocular cells and permissive condition of nucleic acid uptake for the treatment of dry eye condition.

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any transgene can be expressed in ocular cells of human at minimum effective levels for therapeutic response. The specification does not provide any specific guidance for expressing the nucleic acid Seq ID no 1 or 3 in ocular cells of postmenopausal women. In fact, the art of gene therapy at the time of the filing of this application was unpredictable wherein any gene was expressed in an individual suffering from dry eye or other ocular disease. Furthermore, the state of the prior art effectively summarized by the references of Verma and Somia (1997) Nature 389:239-242 and Pfeifer and Verma (2001) Annual Review of Genomics and Human Genetics.2: 177-211 describes progress made in developing new vectors and also suggest vector targeting *in vivo* to be unpredictable and inefficient. Verma et al., reviews various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of claimed invention resolution to vector targeting had not been achieved in the art (Verma et al., 1997; Pfeifer et al., 2001; entire article). They highlight some advantages of using retroviral and adeno-associated viral vector in gene therapy but also acknowledge a greater level of skepticism in using these vectors in human (Pfeifer et al., 2001; abstract). It is noted by the authors that more efficient and safe vectors are required to deliver gene to the target cell for therapeutic effective level of gene expression (Pfeifer and Verma 2001, Annual Review of Genomics and Human Genetics.2: 177-211, pp 201).

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples only describes that 15-Lipoxygenase can be expressed in eye. Specifically, Example 1 demonstrates that RP-HPLC analyses of conjunctiva samples showing moderate activity in seven out of 21 samples. They used four samples that were positive for 15- LO activity for RT-PCR analyses. The results showed only one out of four positive for 15-LO-1 and one sample positive for both isoenzyme.

It is also not clear from the specification whether this example used tissues derived from *ex-vivo* or *in vivo* experiment. In addition Applicant do not provide disclosure on type of vector and method of delivering that vector to express transgene in the subject. Furthermore, it is not enough to reasonably predict that the transgene can be expressed using vectors via any route of administration at reasonable level for appropriate time duration at appropriate cells of eye for the treatment of dry eye conditions in human or any veterinary patients. Because of the art, as shown above, does not disclose how the claimed vectors would be effective in all postmenopausal patients, the Artisan could not predict, in the absence of proof to the contrary, that such applications as Applicant claims would be efficacious in therapeutic treatment. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (1) how an artisan of skill would have practiced the claimed method in any patient (ii) the claimed method would have resulted in expression of 15-lipoxygenase in amount sufficient to treat the dry eye

conditions administering via drop or ointment in "any patient". An artisan would have to carry out extensive experimentation to make use the invention, and such experimentation would have been undue because of the art of gene therapy and gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

Next, the claims (9-14 and 18-22) recite vectors and plasmid for delivering transgene in ocular cells. It is noted that Stechschulte, et al. (2001) Investigative Ophthalmology & Visual Science: 42(9): 1975-1979 (IDS), teach efficacy and safety of naked plasmid gene therapy to the corneal stroma and epithelium of mice. Corneal injection of the plasmid containing VEGF cDNA induced neovascularization in mice. However, authors also conclude that how broadly these technique would be applied could be determined only by ongoing work in the art (pp 1978, last paragraph). Thus, while art of record teaches administration of naked DNA to cornea in ocular disease of mice, there findings cannot be extrapolated for the treatment of dry eye condition of a patient as neither art nor specification provide specific guidance how to achieve levels and duration of expression needed in these subject for therapeutic response.

It is noted that Behrens, et al. (2002) Investigative Ophthalmology & Visual Science: 43(4): 968-977, teaches *in vivo* efficacy and safety of ophthalmic topical treatment of a retroviral vector bearing an antiproliferative dominant negative mutant cyclin G1 (dnG1) construct in corneal haze after phototherapeutic keratectomy (PTK) in rabbit. In addition, Kamata et al., (Mol Ther. 2001, 4(4): 307-312) teach adenovirus-mediated transduction efficiency in mouse eyes using an adenoviral vector expressing

E. coli β-galactosidase. It is emphasized that they failed to transfer gene onto the cornea by administering drops of a solution containing adenovirus AxCALacZ. However, direct injection of adenovirus expressing AxCALacZ into the anterior chamber resulted in Lac Z expression in the inner layer of cornea (pp 308, 3rd paragraph).

Martin, et al. (2002) Methods: 267-275, evinces an optimistic outlook for the treatment of ocular disorder using adneo-associated viral vector (AAVV), but also acknowledges that the art is not yet generally enabling for humans (pp 268 3rd paragraph). It is noted that Martin et al (Methods 2002: 267-275) emphasize that efficiency of transfection of specific cell types of eye are dependent on a number of variables including the site of injection, the AAV serotype and titer and the amount of DNA (pp 268-269). The specification does not provide any specific guidance to address these issues.

However in the case of dry eye condition, the results of Stechschulte, et al. or Behrens et al., or Kamata et al. or Martin, et al. cannot be predictive of treating deficiency of 15-lipoxygenase in treating dry eye condition of any patient because above described genes are used in animal model for different cause, diseases and cannot be extrapolated to human. In fact recently Barabino et al., (Investigative Ophthalmology & Visual Science. 2004,45(6): 1641-1646) two years after filing of this application state that "in spite of mouse being attractive model due to availability and ease of knockout and transgenic strains all the existing animal models of dry eye mimic different pathogenic mechanisms of Dry eye syndrome, or keratoconjunctivitis sicca (KCS) and at the moment none of them seems to mirror precisely the complexity and chronicity of

this frequent and debilitating condition" (pp1645; Conclusion). This clearly establishes the unpredictability of the animal models currently being used for evaluating therapeutics effective against dry eye and thus findings in mouse model cannot be directly extrapolated to human situations.

Furthermore, It is noted that, the specification does not teach whether viral vectors or plasmid can be used effectively in administering transgene either via any or topical route in patients. The specification also does not provide any guidance as to how studies in animal model can be extrapolated to human situations. In addition, prior art at the time of filing of this application as described before did not provide any convincing guidance in this regard either.

The cited arts clearly indicate an unpredictable status of the gene therapy art pertaining to treatment of dry eye condition. Although, specific vectors, promoters, genes, and route of administration might be or may have been effective for treatment of specific disease providing specific therapeutic effect. Gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest, which results in a therapeutic effect.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions commensurate with the full scope of the claims. The specification and prior art do not teach a method of *in vivo* delivery of a gene such that it is expressed at therapeutic effective level for desired duration in the eye of a

postmenopausal women suffering from dry eye condition. An artisan of skill would have required undue experimentation to develop/design a suitable vector and practice the method as claimed because the art of gene therapy, vector design and *in vivo* delivery and treatment of dry eye condition in general by gene delivery *in vivo* was unpredictable at the time of filling of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Cuthbertson, R.A. (US Patent 6,204,251, dated 3/20/2001, effective priority date 10/31/1994; IDS) in view of Brash et al., (2002; Proc. Natl. Acad. Sci. USA: 94, pp. 6148–6152; IDS), Liminga et al., (Biochim Biophys Acta. 1994 20; 1210(3): 288-96); Yanni et al., (US Patent 5,696166; dated 12/9/1997; IDS), Peterson et al., (JAMA 287(5): 585-586).

Cuthbertson R.A (US Patent 6,204,251) describes method of treating ocular disease conditions using exogenous nucleic acid into ocular cells such that the protein is expressed and the condition is treated. Specifically, the patent teach method of treating ocular disease including dry eye condition (column 10 and column 5; 3rd

paragraph) when exogenous nucleic acid is introduced into an ocular cells under condition permissive for uptake including via topical application (column 9, 2nd paragraph). In addition, inventor demonstrates extensive β-galactosidase marker gene expression, when β-galactosidase-expressing recombinant adenoviral vector is introduced topically in debrided corneal epithelia cells of rats. (Columns: 8-9, example 1). Claims 1-7; recite that the trasngene (Ref Seq Id 1-3) is administered in a patient suffering from dry eye such that it is expressed in corneal cells and the patient is treated. Claims 8-22 recite number of vector that could be used to deliver the transgene. It is noted that claimed invention has two steps; method of treating dry eye and method of delivering transgene and the cited reference has similar limitations. Cited patent also teaches treatment of variety of other ocular disorder by delivering exogenous nucleic acid encoding a protein that is useful in the treatment of ocular diseases. However Cuthbertson do not teach treatment of dry eye condition in postmenopausal women by expressing 15-lipoxygenase-1, -2 (Ref seq ID 1 or 3).

Peterson et al., describes factors that cause dry eye conditions in postmenopausal women (pp 585-586, refer entire letter). However, Peterson et al does not teach how dry eye conditions could be treated.

Brash et al., 2002; Proc. Natl. Acad. Sci. USA: 94, pp. 6148–6152 teaches the presence of 15-lipoxygenase mRNA in cornea (Abstract). The presence of 15-lipoxygenase cDNA in cornea was in accordance with the metabolic studies, wherein it was established that human cornea synthesizes 15*S*-HETE from [14C] arachidonic acid (Liminga et. al., pp294, 4th paragraph, pp295 line 7-11). However, neither of these

studies describes the role of 15-lipoxygenase-1-2 or 15-HETE in the treatment of dry eye.

Yanni et al. teaches compositions that include 15-HETE in therapeutic effective amount for the production of mucins. The compositions are administered topically for the treatment of dry eye (US Patent 5,696166; Column 3, 2nd paragraph). However, Yanni et al., does not teach use of a transgene in a vector that could be expressed in-patient suffering from dry eye.

At the time of invention, it would have been obvious to an artisan of skill to administer a composition containing a nucleic acid of Seq ID no 1 or 3 (15-lipoxygenase-1 or -2) in an ocular drop to an eye of a non-human mammal for the treatment of dry eye with a reasonable expectation of success. An artisan would have been motivated at the time of invention to treat a non human mammal by administering genes associated with arachidonic acid (AA) metabolites using appropriate vector for the treatment of dry eye condition because Peterson et al., describe prevalence of dry eye conditions in postmenopausal women. Liminga et al., teaches presence of 15-lipoxygenase in cornea which also synthesizes 15(s)-HETE. Yanni et al., teaches compositions that include 15-(s)-HETE for the mucins production that in turn increases tear production. It is noted that it would have been obvious to one of ordinary skill to combine the trangene such as 15-lipoxygenase or its isoform that could be expressed in the ocular cells of a non-human mammal, using vector and conditions described by Cuthbertson, R.A. (US Patent 6,204,251, dated 3/20/2001, effective priority

date10/31/1994) to increase the production of mucin which would have resulted in more tear production in eye.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1 is indefinite because the method does not recite a positive step linking the preamble to the steps of the claimed method.

Claims 6-8 and 15-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-8 and 15-16 are improperly dependent claims because they depend on themselves. Appropriate correction is required.

8. No Claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anoop Singh
Examiner, AU 1632

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER